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10/587,523	03/07/2007	Nadia Mastroianni	100506-00028	9518

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EXAMINER
PROUTY, REBECCA E

ART UNIT	PAPER NUMBER
1652	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/587,523	MASTROIANNI ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *6-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 July 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Applicant's election with traverse of Group VI, claims 1-5 drawn to a clytin photoprotein variant having a $G_{142}\rightarrow C$ substitution (i.e., SEQ ID NO:7) in the reply filed on 11/5/09 is acknowledged. The traversal is on the ground(s) that the inventions of Groups I-XLV relate to a single general inventive concept under PCT Rule 13.1, as they contain a special technical feature not disclosed in the cited reference of Lambolez et al., i.e., the instantly claimed clytin photoprotein variants are characterized by enhanced bioluminescence (higher intensity of light emission). This is not found persuasive because the specification does not establish that each of the claimed clytin variants in fact have this property compared to SEQ ID NO:1 (wild type) and even if it could be shown to be the case while the variants of Lambolez et al. cited in the prior action may not disclose photoprotein variants having enhanced bioluminescence, this also is not a special technical feature as defined by PCT Rule 13.2 as it also is taught in the prior art and/or obvious therefrom. For example Tsuzuki et al. and Prasher (US Patent 5,360,728) each teach aequorin variants having enhanced bioluminescence. Furthermore, a skilled artisan would have found it obvious to use the methods of producing aequorin variants having enhanced bioluminescence taught by Tsuzuki et al. to modify the clytin protein of Inouye et al.

with the expectation that doing so would produce clytin variants with enhanced bioluminescence.

The requirement is still deemed proper and is therefore made FINAL.

Claims 6-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/05/09.

Claims 1-5 are objected to as reciting non-elected subject matter.

Claims 1-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (upon which claims 2-5 depend) is indefinite in the recitation of "functional derivative" as the specification does not define what structural and functional properties must be present within a protein to be within the scope of this phrase.

Claims 1 and 5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The purpose of the written description requirement is to ensure that the inventor had possession, at the time the invention was made, of the specific subject matter claimed. For a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

MPEP § 2163 further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the biomolecule, it is "not sufficient characteristic for written description

purposes, even when accompanied by a method of obtaining the claimed biomolecule."

The factors considered in the Written Description requirement are (1) level of skill and knowledge in the art, (2) partial structure, (3) physical and/or chemical properties, (4) functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the (5) method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163.

These claims are directed to a genus of clytin variants and functional derivatives thereof. Furthermore, the specification provides no basis for understanding what the scope of the term "functional derivatives" encompasses. As such the claims could be reasonable interpreted as encompassing any photoprotein as there are no clear structural or functional limitations recited. The specification teaches the structure of only a few representative species of such clytin variants. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of having photoprotein activity. Given this lack

of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 1 and 5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for clytin variants having 90% identity to SEQ ID NO:1 and comprising a G_{142}→C substitution at the position corresponding to G_{142} of SEQ ID NO:1, does not reasonably provide enablement for any functional derivative of a clytin variants having 90% identity to SEQ ID NO:1 and comprising a G_{142}→C substitution at the position corresponding to G_{142} of SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 1 and 5 are so broad as to encompass a genus of clytin variants and functional derivatives thereof. Furthermore, the specification provides no basis for understanding what the scope of the term "functional derivatives" encompasses. As such the claims could be reasonable interpreted as encompassing any photoprotein as there are no clear structural or functional limitations recited. The

scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of photoproteins broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a few specific clytin variants (i.e., SEQ ID NOS:2-10).

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish

with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass any functional derivative of a clytin variants having 90% identity to SEQ ID NO:1 and comprising a G_{142}→C substitution at the position corresponding to G_{142} of SEQ ID NO:1, i.e., any photoprotein because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting photoprotein activity; (B) the general tolerance of photoproteins to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any functional derivative of a clytin variants having 90% identity to SEQ ID NO:1 and comprising a G_{142}→C substitution at the position corresponding to G_{142} of SEQ ID NO:1. The scope of the claims must bear a

reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of clytin variants having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Prasher (US Patent 5,360,728).

Prasher teach several aequorin variants having enhanced bioluminescence compared to wild type aequorin. These variants can be considered to be "functional derivatives" of the clytin variant of SEQ ID NO: 7.

Claim 1 is rejected under 35 U.S.C. 102(a) as being anticipated by Tsuzuki et al.

Tsuzuki et al. teach several aequorin variants having enhanced bioluminescence compared to wild type aequorin. These

variants can be considered to be "functional derivatives" of the clytin variant of SEQ ID NO: 7. While Tsuzuki et al. was published after one of applicants claimed foreign priority documents (EPO 05005390.9), the priority document does not provide support for the current claims as it does not disclose variant ix) of claim 1. As such applicants cannot rely on the benefit of the filing date of the prior application.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over either of Prasher (US Patent 5,360,728) or Tsuzuki et al.

Each of Prasher and Tsuzuki et al. teach aequorin variants having enhanced bioluminescence compared to wild type aequorin.

They do not specifically teach the addition of a mitochondrial targeting sequence to the amino terminus of said variants. However, the use of photoproteins as reporter proteins for calcium concentrations in various subcellular localities is well known in the art as are targeting sequences for most subcellular organelles (i.e., nuclear localization signals, mitochondrial localization signals, ER targeting signals, peroxisome targeting signals, etc.). Therefore it would have been obvious to one of ordinary skill in the art to fuse the aequorin variants of Prasher or Tsuzuki et al. to a subcellular targeting sequence in order to use the variants as a reporter protein for calcium concentrations within these organelles.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The fax phone number for this Group is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Rebecca Prouty/
Primary Examiner
Art Unit 1652